

Applicants: Rothberg, et al.
U.S.S.N. 09/814,338

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-55. (Withdrawn)

56. (Currently amended) A substrate for analyzing a nucleic acid, the substrate comprising:

a cavitated fiber optic wafer formed from a fused bundle of a plurality of individual optical fibers, each individual optical fiber having a diameter between 3 and 100 μm , the wafer comprising a top surface and a bottom surface, the top surface comprising at least 10,000 wells, wherein said wells are etched into the top surface of the cavitated fiber optic wafer and wherein the thickness of the wafer between the top surface and the bottom surface is between 0.5 mm and 5.0 mm in thickness; and wherein the depth of each well ranges from between one half the diameter of an individual optical fiber to and three times the diameter of an individual optical fiber; and wherein a plurality of wells on the top surface of the cavitated wafer have a nucleic acid disposed therein; and

a plurality of beads disposed within wells on the top surface of the cavitated wafer, wherein each bead has said beads having a pyrophosphate sequencing reagent attached thereto.

57. (Currently amended) The substrate of claim 56, wherein the nucleic acid sequence is an anchor primer immobilized on the wells or on said beads.

58. (Currently amended) The substrate of claim 56, wherein the substrate comprises a plurality of fiber optic surfaces the diameter of each individual optical fiber in the cavitated wafer is between 6-50 μm .

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59. (Currently amended) The substrate of claim 58, wherein the fiber optic surface includes two or more ~~anchoring primers~~ nucleic acids separated by approximately 10 μm to approximately 200 μm .

60. (Currently amended) The substrate of claim 58, wherein the fiber optic surface includes two or more ~~anchoring primers~~ nucleic acids separated by approximately 10 μm to approximately 150 μm .

61. (Currently amended) The substrate of claim 58, wherein the fiber optic surface includes two or more ~~anchoring primers~~ nucleic acids separated by approximately 150 μm .

62.-63. (Cancelled)

64. (Currently amended) The substrate of claim 56 wherein the wafer further comprises 10^3 or more groups of ~~oligonucleotides~~ nucleic acid sequences in said wells.

65. (Currently amended) The substrate of claim 64, wherein said substrate comprises 10^4 or more different groups of nucleic acid sequences in discrete known regions.

66. (Currently amended) The substrate of claim 64, wherein said substrate comprises 10^5 or more different groups of ~~oligonucleotides~~ nucleic acid sequences with known sequences in discrete known regions.

67. (Currently amended) The substrate of claim 64, wherein the ~~groups of~~ oligonucleotides nucleic acid sequences are attached to the ~~surface~~ wells or beads by a linker.

68. (Currently amended) The substrate of claim 64, wherein the ~~groups of~~ oligonucleotides nucleic acid sequences are covalently attached to the ~~surface~~ wells or beads.

69.- 83. (Cancelled)

84. (Currently amended) An apparatus for processing a plurality of nucleic acids, the apparatus comprising:

a flow chamber having disposed therein a cavitated fiber optic wafer surface;

a cavitated fiber optic wafer formed from a fused bundle of a plurality of individual optical fibers, each individual optical fiber having a diameter between 3 and 100 μ m, the wafer comprising a top surface and a bottom surface, the top surface comprising at least 10,000 wells, wherein said wells are etched into the top surface of the cavitated fiber optic wafer and wherein the thickness of the wafer between the top surface and the bottom surface is between 0.5 mm and 5.0 mm in thickness; and wherein the depth of each well ranges from between one half the diameter of an individual optical fiber to and three times the diameter of an individual optical fiber; and wherein a plurality of wells on the top surface of the cavitated wafer have a nucleic acid disposed therein;

a plurality of beads disposed within wells on the top surface of the cavitated wafer, wherein each bead has said beads having a pyrophosphate sequencing reagent attached thereto;

fluid means for delivering pyrophosphate sequencing reagents, including sequential delivery of nucleotide triphosphates, from one or more reservoirs to the flow chamber so the nucleic acids disposed on beads in the wells on the top surface of the fiber optic wafer are exposed to the reagents; and

detection means for detecting optical signals from each well, wherein said detection means is in communication with the wells, each optical signal being indicative of reaction of the pyrophosphate sequencing reagents with the nucleic acid in a well.

85. (Currently amended) The apparatus of claim 85 84, wherein said detection means further comprises signal tracking means for correlating said optical signals from each of said microparticles wells in each of said digital images to form for each said

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~~microparticle of said plurality a sequence of said optical signals the diameter of each individual optical fiber in the cavitated wafer is between 6-50 μ m.~~

86. (Previously amended) The apparatus of claim 85, wherein said detection means is a CCD camera.

87. (Currently amended) The apparatus of claim 86 ~~84~~, wherein said analyte ~~the nucleic acid~~ is DNA.

88. (Previously added) The substrate of claim 56 wherein the substrate has a polished fiber optic surface opposite to the cavitated fiber optic surface.

89. (Previously added) The substrate of claim 88 wherein the polished surface allows for optical coupling to a second optical fiber.

90. (Currently amended) The substrate of claim 56 wherein the cavitated ~~surface fiber optic wafer~~ is coated.

91. (Previously added) The substrate of claim 90 wherein the coating is selected from the group consisting of plastic, gold layers, organosilane reagents, photoreactive linkers, hydrophilic polymer gels and plronic polymers.

92. (Previously added) The substrate of claim 56 wherein said sequencing reagent is luciferase.

93. (Previously added) The substrate of claim 56 wherein said sequencing reagent is sulfurylase.

94.-95. (Cancelled)

96. (Currently amended) The ~~array apparatus~~ of claim 69 ~~84~~ wherein the cavitated ~~fiber optic wafer surface~~ is coated.

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97. (Currently amended) The array apparatus of claim 96 wherein the coating is selected from the group consisting of plastic, gold layers, organosilane reagents, photoreactive linkers, hydrophilic polymer gels and pluronic polymers.

98. (Currently amended) The array apparatus of claim 69 84 wherein said sequencing reagent is luciferase.

99. (Currently amended) The array apparatus of claim 69 84 wherein said pyrophosphate sequencing reagent is sulfurylase.